REMARKS

Reconsideration of this application is respectfully requested. Claims 5 and 31 have been amended. New claims 34 and 35 have been added. Claims 1-6, 20, 22-25, 31, 34, and 35 are pending and at issue.

Claim 5 has been amended to correct a typographical error. Claim 31 has been amended to specify that the dose of conjugated equine estrogen is administered to a human. Support for this amendment is found in the specification at, for example, page 19, lines 6-9. No new matter has been added.

The specification has been amended to correct typographical errors in the Table at page 24, lines 5-24. In particular, the Table on page 24 has been amended to correct the entries for the median and mean serum E2 levels of the intact and ovx animals. One of ordinary skill in the art would readily appreciate that these entries are reversed, because the specification discloses that the ovx group exhibited lower serum E2 levels than the intact group (*see* Specification at p. 23, lines 12-13; and Fig. 1A). One of ordinary skill would also understand that this is an obvious error, particularly in view of Fig. 1A, which corresponds to this Table and shows the ovx animals having the lowest serum E2 level and the intact animals having the next lowest level. *See* MPEP §2163.07 II (Obvious Errors). No new matter has been added.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-6, 20, 22-25, and 31 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement based on various grounds, as discussed below.

The rejection is respectfully traversed, and reconsideration is requested.

The Examiner states that the specification does not enable the method of claim 1 because there is no evidence that *in vivo* administration of any estrogen compound can reduce Aβ levels without affecting sAPP levels, but acknowledges that this method is enabled with respect to 17β-estradiol. *See* Office Action at pp. 2-3. Contrary to the Examiner's statement, the specification discloses how to make and use all the estrogen compounds of the invention, and provides disclosure of pharmaceutical formulations, administration, dosage, and regimen. *See* p. 15, line 10 to p. 19, line 27. Furthermore, those of ordinary skill in the art consider 17β-estradiol representative of a larger class of estrogens, as evidenced by U.S. Patent No. 5,554,601 ("the '601 patent"), for example, which bases its conclusions on the efficacy of a broad class of estrogen compounds on its *in vivo* studies involving the administration of 17β-estradiol. *See* '601 patent at col. 15, line 34 to col. 17, line 33 (Example 3). Thus, the disclosure in the specification providing a detailed description of how to make and use estrogen compounds, along with the exemplary support (e.g., regarding 17β-estradiol) would enable one of ordinary skill in the art to make and use the full scope of the claimed invention (i.e., the broad class of estrogen compounds defined at page 8, lines 6-17 of the specification) without undue experimentation.

The Examiner states that the specification provides inadequate guidance as to how to determine the amount of compound that would reduce Aβ levels and not affect sAPP levels. Office Action at p. 3. Contrary to the Examiner's statement, the specification provides significant disclosure regarding dosage and regimen. *See* p. 17, line 13 to p. 19, line 27. This disclosure indicates that an effective dose of estrogen compound will depend on various parameters, "which can be readily determined according to standard good medical practice by those of skill in the art." *See* p. 17, lines 14-19. Additionally, the specification expressly defines an "Aβ level reducing dose"

and provides exemplary dosages suitable for all animals, ranging from about 0.5 μg estrogen per kg body weight (μg/kg) to about 50 mg/kg. *See* p. 18, lines 18-27. Further, one of ordinary skill would be able to determine the required dose by performing standard assays disclosed in the specification. *See* p. 15, lines 4-8. For instance, methods of screening for a dose of estrogen compound having the ability to reduce Aβ levels are described in Examples 1 and 2 (*see* p. 20, line 4 to p. 29, line 4; and p. 29, lines 6-11); and determination of sAPP levels is described at p. 21, line 17 to p. 22, line 2. Such techniques are well within the abilities of a person of ordinary skill in the art and would not require undue experimentation. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003) ("The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'").

The Examiner states that the specification does not disclose how to predict susceptibility to Alzheimer's Disease (AD). Office Action at p. 3. However, according to the specification, reduced estrogen levels *in vivo* result in increased amyloid production, which allows one to predict whether a given subject will be more susceptible to developing AD. *See* p. 14, lines 13-18. It is well established that the PTO should "presume that a statement of utility made by an applicant is true." *See* MPEP §2107.02(III)(A). Here, the Examiner has provided no basis for doubting the veracity of the specification. Moreover, the specification expressly defines "has an increased risk of developing" and "shows a symptom of" a disease or disorder associated with amyloidosis (p. 18, lines 8-17). These definitions describe specific subjects who are susceptible to developing AD, such as those with a genetic predisposition to develop amyloidosis, or those in their 70s and 80s. Thus, the specification provides adequate guidance for predicting AD susceptibility.

The Examiner states that the specification does not disclose how estrogen treatment would delay, reduce the likelihood of, or ameliorate AD or other diseases associated with amyloidosis. Office Action at p. 3. However, an inventor is not required to disclose or even know the mechanism of action behind his invention. *See Cross v. Iizuka*, 753 F.2d 1040, 1042 (Fed. Cir. 1985) ("it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement"). Nevertheless, the specification discloses the inventors' discovery that estrogen compounds reduce Aβ levels *in vivo*. *See* p. 7, lines 15-19; and p. 20, line 4 to p. 29, line 4 (Examples 1 and 2). Since Aβ peptides are a major component of amyloid deposits, by which AD is characterized, there is sufficient support for using estrogen compounds in connection with diseases associated with amyloidosis.

The Examiner states that undue experimentation would be required to identify estrogen compounds that reduce Aβ levels without affecting sAPP levels. Office Action at p. 3. Yet, as discussed in detail above, the specification discloses how to screen for estrogen compounds having the ability to reduce Aβ levels and how to determine sAPP levels by using techniques well known to those of ordinary skill.

The Examiner states that treatment of AD is unpredictable because Heikkinen et al. (*Exp. Neurol.*, 187(1):105-17 (2004)) teaches that estrogen treatment does not affect beta amyloid accumulation and plaque formation. Office Action at p. 3. However, the question of enablement involves consideration of the state of the prior art (i.e., what one skilled in the art would have known) at the time the application was filed. MPEP §2164.05(a). Heikkinen was published after the

filing date of the present application. Thus, the teachings of Heikkinen are irrelevant as to whether or not the present claims are enabled.

The Examiner states that the results in the specification (p. 24 Table and Fig. 2A) are confusing because the Aβ level for intact animals is lower than that for the low and high dose ovx+E2 animals, which allegedly makes it unclear how one of ordinary skill could screen for estrogen compounds that reduce Aβ levels, and then extrapolate the results to enable the claimed methods. Office Action at pp. 3-5. In the present application, Fig. 2A shows brain Aβ levels for low and high dose ovx+E2 animals that are lower than brain Aβ levels for ovx animals, and that this difference is statistically significant. The data represented in Fig. 2A indicate that estrogen deprivation (i.e., in the ovx group) leads to increased Aβ levels, and that estrogen replacement (i.e., in the ovx+E2 groups) reverses this condition. The intact group is a control group, and the major statistical analysis conducted on the Fig. 2A data is based on comparisons between the ovx group and the three other groups. *See* Specification at p. 22, lines 8-13. Thus, the results in the specification are clear and show that estrogen treatment lowers Aβ levels. Additionally, as discussed in detail above, the specification discloses how to screen for estrogen compounds that reduce Aβ levels by using well known techniques and assays. Moreover, compound screening need not be enabled for claims 20 and 22-25, because these claims are limited to 17β-estradiol. Since the present inventors found that estrogen compounds, such as the representative 17β-estradiol, can reduce Aβ levels, and that Aβ deposition plays a central role in AD pathology (specification at p. 2, lines 19-27), one of ordinary skill could have readily extrapolated the disclosed *in vivo* results to make and use the claimed methods.

The Examiner states that Zandi et al. (*JAMA*, 288(17):2123-29 (2002)) does not show that estrogen therapy is useful in the prevention of AD because it concludes that there is no benefit of hormone replacement therapy (HRT) unless used for over 10 years. Office Action at p. 5. However, it appears that the Examiner has focused on only one conclusion of the Zandi study without considering all the data. Figures 2A and 2B (p. 2127), for instance, show that all the women studied (i.e., not just those who used HRT for over 10 years) had a reduced risk of developing AD. While the risk reduction was most dramatic for women who used HRT for over 10 years, Figure 2B clearly shows that the risk was, in fact, reduced in HRT nonusers and women who used HRT for less than 3 years or 3-10 years. Hence, Zandi confirms that estrogen therapy effectively delays or reduces the likelihood of AD. Further, the data collected from women who used HRT for over 10 years provides significant evidence that estrogen can delay or reduce the risk of AD since it effectively reduced this risk for an entire 10 year period. Thus, a benefit was achieved for the full duration (not just at the 10-year mark) because the risk of AD remained relatively low. If anything, the 10-year delay described in Zandi underscores that estrogen is highly effective at delaying, reducing the likelihood of, or ameliorating, AD, as called for in pending claims 20 and 22-25.

The Examiner states that the differences observed for sAPP levels in Fig. 3 are insignificant, which implies that even physiological amounts of estrogen do not affect APP levels. Office Action at p. 5. It appears that the Examiner is misinterpreting Fig. 3 because a significant aspect of this figure is the level of sAPP in the ovx+E2 animals *as compared to* the level of sAPP in the intact animal. According to Fig. 3, these levels are the same, thereby demonstrating the inventors' surprising discovery that the level of sAPP is not affected by administration of an estrogen compound.

In view of the foregoing, the present specification fully enables one of ordinary skill in the art to make and use the invention called for in claims 1, 2, 4-6, 20, 22-25, and 31 without undue experimentation. Accordingly, applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 31 has been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, this claim is "inconsistent with claim 1" because claim 1 applies to all animals, and there is no indication that the dosages of conjugated equine estrogen recited in claim 31 would be effective in all animals.

The definiteness requirement is satisfied if a person of ordinary skill would understand the scope of the claim when read in view of the specification. Here, one of ordinary skill would readily comprehend that claim 31 encompasses the method of claim 4, wherein the dose of conjugated equine estrogen is selected from an amount expressly recited in the claim. Nevertheless, to expedite prosecution of the application, claim 31 has been amended to read: "... wherein the dose of conjugated equine estrogen is administered to a human and is selected from ...." *See* Specification at p. 19, lines 6-9.

In view of the foregoing, claim 31 is not indefinite. Accordingly, applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 20 and 22-25 have been rejected under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 5,554,601 ("the '601 patent"). This patent is cited by the Examiner as disclosing a method of treating a neurodegenerative disorder by administering 17β-estradiol. Additionally, according to the

Examiner, "the mechanism by which estradiol exerts its activity has no patentable significance." Office Action at p. 6.

The rejection is respectfully traversed, and reconsideration is requested.

For a reference to be anticipatory, it must teach each and every limitation of the claim. *See* MPEP §2131. Here, the '601 patent does not teach the claimed dosage amount - i.e., "an Aβ level reducing dose of 17β-estradiol." Contrary to the Examiner's contention, the mechanism of action of 17β-estradiol is central to the patentability of these claims because it is determinative of the required dosage amount, which is defined in terms of the result it achieves. It is well established that functional limitations may be used to set clear boundaries on the patent protection sought. *See* MPEP §2173.05(g) ("A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step."). Thus, this limitation should not be ignored.

The '601 patent makes no reference to Aβ levels, and thus provides no teaching on what amount of 17β-estradiol would constitute an Aβ level reducing dose. *See In re Burt*, 356 F.2d 115, 121 (CCPA 1965) ("Silence in a reference is hardly a proper substitute for an adequate disclosure of facts"). Further, the dose disclosed in the '601 patent is not encompassed by the definition of "Aβ level reducing dose" (*see* Specification at p. 18, lines 18-27), and would not necessarily achieve the claimed result of reducing Aβ. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (to establish inherency, the reference "must make clear that the missing descriptive matter is necessarily present"). Additionally, the '601 patent does not disclose any ratios of Aβ42 to Aβ40, as called for in claim 25. Hence, this reference does not disclose the method of claim 25. Accordingly, applicant respectfully requests that this rejection be withdrawn.

* * * * *

Claims 20 and 23-25 have been rejected under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 5,719,137 ("the '137 patent"). The Examiner states that the '137 patent discloses a method of reducing the risk of AD by administering 17α-dihydroequilenin, and describes an animal study in which groups of rats were treated with 17β-estradiol for up to three days.

The rejection is respectfully traversed, and reconsideration is requested.

The '137 patent does not disclose Aβ levels or ratios of Aβ42 to Aβ40. As discussed above with respect to the '601 patent, the '137 patent also fails to expressly or inherently disclose the claimed dosage amount, which is a functional claim limitation defined in terms of its result. In view of the foregoing, the '137 patent does not anticipate claims 20 and 23-25. Accordingly, applicant respectfully requests that this rejection be withdrawn.

* * * * *

Claims 1-3, 5, 6, 20, 23-25, and 31 have been rejected under 35 U.S.C. § 102 as anticipated by International Publication No. WO 98/43647 ("WO '647"). According to the Examiner, WO '647 teaches the administration of 17β-estradiol to reduce APP fragments, which include Aβ, and teaches methods for alleviating an impaired condition brought on by neurodegenerative or cognitive changes. Office Action at p. 7.

The rejection is respectfully traversed, and reconsideration is requested.

WO '647 discloses a method for treating neurodegenerative disorders by reducing APP holoprotein levels through administration of estrogenic compounds, such as 17β-estradiol. *See, e.g.*, WO '647 at p. 1, lines 13-23; p. 6, lines 1-2 and 15-17; and p. 8, lines 25-26. WO '647 does not disclose Aβ levels or ratios of Aβ42 to Aβ40. Thus, as discussed above with respect to the '601 and

'137 patents, WO '647 also fails to expressly or inherently disclose the claimed dosage amount, which is a functional claim limitation defined in terms of its result.

Additionally, WO '647 does not disclose a method involving reduction of Aβ levels because WO '647 is limited to a method of reducing APP holoprotein, which is a full-length, native peptide that has not yet undergone proteolytic cleavage. APP holoproteins are not Aβ peptides, which are generated by proteolytic processing of APP through β- and γ-secretase activities (*See* Specification at p. 1, line 11 to p. 2, line 9). Reduction of APP holoprotein is not indicative of reduced Aβ levels. In fact, the present specification states that "a change in sAPPα levels (up or down) is a poor guide to anti-amyloid drug development", and describes the present inventors' surprising discovery that administration of estrogen compounds reduces Aβ levels, without affecting sAPP levels (p. 7, lines 15-22). Thus, reduced APP levels does not necessarily correlate to reduced Aβ levels. WO '647, which makes no mention of Aβ levels, thus fails to teach the presently claimed methods.

In view of the foregoing, WO '647 does not anticipate claims 1-3, 5, 6, 20, 23-25, and 31. Accordingly, applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claim 22 has been rejected under 35 U.S.C. § 103(a) as obvious over the '137 patent or WO '647. The Examiner acknowledges that each of these references fails to disclose administration of 17β-estradiol for at least 10 days, but contends that this dosing regimen would be obvious to one of ordinary skill. The Examiner also reiterates his contention that the mechanism of estradiol is not significant.

The rejection is respectfully traversed, and reconsideration is requested.

Neither the '137 patent nor WO '647 teaches or suggests "an Aβ level reducing dose of 17β-estradiol," as presently claimed. Contrary to the Examiner's contention, the mechanism of action of 17β-estradiol has patentable significance that cannot be ignored since the claimed dosage amount is a functional limitation defined in terms of its result. Since neither the '137 patent nor WO '647 makes any mention of Aβ levels, neither reference teaches or suggests a dosage amount in which such levels are reduced.

Furthermore, the '137 patent expressly teaches away from the use of 17β-estradiol, which is alleged to have serious disadvantages not found in treatments using 17α-dihydroequilenin. For instance, according to the '137 patent, 17β-estradiol causes negative uterotrophic effects and requires co-administration with progestin to avoid vaginal bleeding and reduce the risk of endometrial carcinoma that result from required high doses of this compound (col. 3, lines 60-65; and col. 4, lines 17-20 and 26-30). Thus, the teachings of the '137 patent would have discouraged one of ordinary skill from administering 17β-estradiol in the claimed method. Where a reference teaches away from the claimed invention, that reference cannot be combined to render the claimed invention obvious. *See* MPEP § 2145; *In re Crasselli*, 713 F.2d 731 (Fed. Cir. 1983).

Additionally, WO '647 does not teach or suggest a dosage amount that reduces Aβ levels because this reference is limited to a method of reducing APP holoprotein, which does not necessarily correlate with a reduction in Aβ levels, as discussed above.

In view of the foregoing, claim 22 is not obvious over the '137 patent or WO '647. Accordingly, applicant respectfully requests that this rejection be withdrawn.

* * * * *

Claims 22 and 23 have been rejected under 35 U.S.C. § 103(a) as obvious over Xu et al., *Nature Medicine*, vol. 4: 447-451 (April 1998) ("Xu"). Xu is cited by the Examiner as disclosing that estradiol reduces neuronal generation of Aβ peptides and is thus "clearly suggestive of delaying or preventing AD." Office Action at p. 9. The Examiner again contends that the estradiol mechanism of action has no significance.

The rejection is respectfully traversed, and reconsideration is requested.

Xu does not teach or suggest a 17β-estradiol dosage that would not affect sAPP levels. Rather, Xu teaches that 17β-estradiol causes an increase in sAPP. Specifically, Xu states, "The estrogen-related diminution in Aβ generation was accompanied by an approximate 30-40% increase in sβAPP release (Fig. 3*a*)" (Xu at p. 449, left column). Claims 22 and 23 call for a dosage amount that constitutes a functional limitation, defined in terms of two results that it achieves: (i) reduction of Aβ levels; and (ii) no affect on sAPP levels. Such functional limitations may be properly used to provide clear boundaries on claim scope, and their patentable significance should not be ignored. *See* MPEP §2173.05(g). Xu fails to teach or suggest this claim limitation, and instead would have discouraged one of ordinary skill from using 17β-estradiol in the claimed methods because doing so would have been expected to raise sAPP levels.

Additionally, to establish obviousness, there must be a reasonable expectation of success in relation to combining or modifying the cited references. *See* MPEP §2142. Here, one of ordinary skill would have had no reasonable expectation that 17β-estradiol could be successfully used *in vivo* based on the Xu teachings. Xu discloses results from *in vitro* studies only. No animal models were used; all results are based on cell cultures. *See* Xu at p. 448. In contrast, claims 22 and 23 are directed to methods comprising administration "to a subject" - i.e., methods having *in vivo* effects.

The present specification addresses the lack of predictive value of *in vitro* results, with particular reference to Xu, by stating, "The *in vitro* results, while promising, are by no means predictive of *in vivo* effects" (Specification at p. 2, lines 19-27 (emphasis added)). Since "patents are written for and by skilled artisans," *see S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1376 (Fed. Cir. 2001), one of ordinary skill would not have reasonably expected that the methods taught by Xu would have been successful "in a subject." At best, Xu may represent an invitation to experiment. However, it is well established that "'obvious to experiment' is not the proper standard for obviousness." MPEP §2145(X)(B). *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988); *see also Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000) ("'obvious to try' is not the standard").

In view of the foregoing, claims 22 and 23 are not obvious over Xu. Accordingly, applicant respectfully requests that this rejection be withdrawn.

* * * * *

Claims 1-6, 20, 22-25, and 31 have been rejected under 35 U.S.C. § 103(a) as obvious over International Publication No. WO 99/48488 ("WO '488") in view of U.S. Patent No. 5,510,342 ("the '342 patent"), U.S. Patent No. 3,843,662) ("the '662 patent") or Lundeen, *Endocrinology*, vol. 138:1552 (1997) ("Lundeen"), individually or taken together. WO '488 is cited by the Examiner as disclosing methods of lowering cholesterol levels that reduce Aβ production and thus decrease the risk of developing AD. Each of the other references are cited by the Examiner as disclosing the use of estrogens to lower cholesterol. According to the Examiner, it would have been obvious to use estrogens in a method of reducing the risk of AD.

The rejection is respectfully traversed, and reconsideration is requested.

None of the cited references teaches or suggests a dosage amount that does not affect sAPP levels. As discussed above, the claimed dosage amount is a functional limitation defined in terms of its result, and this limitation should not be ignored. Since none of the cited references teaches or suggests a dose that achieves the claimed result of not affecting sAPP levels, they cannot be relied on to reject the claims as obvious.

In view of the foregoing, claims 1-6, 20, 22-25, and 31 are not obvious over WO '488 in view of the '342 patent, the '662 patent or Lundeen. Accordingly, applicant respectfully requests that this rejection be withdrawn.

* * * * *

Claim 4 has been rejected under 35 U.S.C. § 103(a) as obvious over WO '647 in view of the '601 patent. WO '647 discloses a method for treating neurodegenerative disorders by reducing APP holoprotein levels using 17β-estradiol. The '601 patent is cited by the Examiner as teaching the equivalence of 17β-estradiol and conjugated equine estrogen, as called for in claim 4. According to the Examiner, it would have been obvious to replace 17β-estradiol with conjugated equine estrogen in view of these references.

The rejection is respectfully traversed, and reconsideration is requested.

Neither WO '647 nor the '601 patent discloses Aβ levels. Thus, these references (taken alone or in combination) do not teach or suggest the claimed dosage amount, which is a functional claim limitation defined in terms of its result - i.e., reduction of Aβ levels.

In view of the foregoing, claim 4 is not obvious over WO '647 in view of the '601 patent. Accordingly, applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 28, 2006

Respectfully submitted,

By Dianna Goldenson

Dianna Goldenson
Registration No.: 52,949
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant